REMARKS

Claims 17-26 are currently pending.

The claims are amended to more particularly state the subject matter which Applicants regard as their invention. None of the amendments constitute new matter. In particular, the amendments to claim 17 part (ii) and claim 21 (a)(ii) are supported by the published application at paragraph 75.

The claims are rejected as anticipated, and/or obvious. For reasons discussed below, it is requested that all the rejections be removed and that the claims be allowed to issue.

1. The Claimed Invention As Compared To The Cited Art

The present claims provide for a therapeutic composition and a drug product comprising the following features:

microparticles, prepared from *activated* platelets, which have been *separated from* the supernatant of the activated platelets; and

one or more extracellular matrix material.

The following table illustrates the differences between the claimed invention and the primary references in the cited art.

	source of microparticles	composition containing microparticles
claimed invention	activated platelets	microparticles separated *from* supernatant
Knighton US Pat. No. 5,165,938	activated platelets	microparticles present *in* supernatant
Chao US Pat No. 5,185,160	freeze-thaw lysed platelets	microparticles present *in* supernatant

2. The Claims Are Not Anticipated By Knighton

Claims 17-21 are rejected under 35 U.S.C. §102(b) as being anticipated by United States Patent No. 5,165,938 by Knighton ("Knighton"). The Examiner contends (i) that the compositions of Knighton contain microparticles, prepared by centrifugation from platelet-rich plasma activated with collagen, mixed with microcrystalline collagen, prepared under sterile conditions from patients not diagnosed with viral diseases, (ii) that the compositions of Knighton contain growth factors PDAF and PDGF, (inherently) fibrinogen and thrombin, as well as inorganic compounds, and (iii) that the compositions of Knighton can be used in conjunction with either biodegradable dressings or other implantable devices.

The Examiner, in the Response to Arguments section of the pending Official Action, states:

> applicants argue that the claimed invention requires collection of "microparticles" from the liquid medium by centrifugation but the cited product is not obtained by separation from the supernatant into which it is released by the activated platelets . . . This is not found true. The cited reference clearly teaches that the activated platelet rich plasma is subjected to a removal of platelets and fibrin by centrifugation and that the resulting supernatant contains molecules or "microparticles."

By the Examiner's own characterization, Knighton teaches centrifugation by which platelets are removed and the supernatant is retained for use. In this regard, Applicants cite Knighton at column 2 lines 39-43:

> The activated PRP containing PDGF and PDAF is preferably added to a biologically compatible macromolecular substance which acts as a carrier. First the platelets are centrifuged at about 950 g and the platelet free supernatant is mixed with the carrier.

This is opposite to the claimed invention, which discards the supernatant and retains the microparticles separated *from* it. The presently claimed invention does not use the supernatant, but rather uses the microparticles separated from the supernatant either by differential centrifugation (where microparticles are in the pellet), filtration or affinity chromatography. This is a substantial difference, as molecules such as cytokines would remain in the supernatant.

Accordingly, Knighton does not teach all the limitations of the claims, and the rejection for anticipation should be removed.

3. The Claims Are Not Anticipated By Chao

Claims 17-21 are rejected under 35 U.S.C. §102(b) as anticipated by United States Patent No. 5,185,160 by Chao ("Chao"). The Examiner contends that Chao teaches a pharmaceutical composition comprising viral-inactivated platelet membrane microparticle fractions "made by activation of platelets by repeated freezing and thawing" and then "separated or collected by centrifugation." Exner et al., 2003, Blood Coag. Fibrinol. 14:773-779 ("Exner") is cited to "evidence the inherent fact that freezing-thawing activates platelets."

Applicants assert that the facts at hand do not satisfy the standard for inherent anticipation. MPEP 2131.01 states:

> "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)

First, like Knighton, Chao uses the microparticle-containing supernatant, while the present invention does not, but rather separates the microparticles *from* the supernatant. Chao states (at column 2 line 66 through column 3 line 9):

> The ghost platelets then are separated from the lysate and are suspended in a solution to form a suspension. Then the suspension containing the ghost platelets is heated to at least 60°C for at least two hours to inactivate viral contaminants. The heat treatment also causes a precipitate to form. . . . the suspension including the precipitate first is homogenized, preferably by sonication, and then the precipitate is separated from the suspension. The suspension then may be stored or used for transfusion.

Further, see Chao at column 4 lines 40-64. Accordingly, Chao cannot anticipate the claimed invention.

Second, Chao does not inherently disclose the activated platelets of the claims. The Abstract of Exner refers to its platelets as activated by freeze-thawing, but (1) there is no basis to assume that the platelets of Chao are necessarily activated, based on Exner; and (2) there is no basis to assume that activation associated with Exner's freeze-thawing is necessarily the same as that presently claimed.

As to point (1), Exner freezes platelet rich plasma at -80°C for one hour then thaws at 37°C once, whereas Chao teaches repeated cycles of freezing at -80°C and thawing at 25°C. As evidenced by Lindemann et al., 2001, J. Cell Biol 154:485-490 (Exhibit A) activated platelets synthesize inflammatory mediators, and Chao's repeated freezing and thawing at sub-metabolic temperatures would not favor such synthesis, even if they would lyse the platelets and free their contents. Thus, there is no basis here to conclude that the freeze-thaw treated platelets of Chao would be activated in the sense of Exner's platelets.

As to point (2), activation caused by different agents has been associated with different activated platelet phenotypes (see Alberio et al., 1998, Br. J. Hematol. 102:1212-1218 (Exhibit B), so that a platelet activated according to Exner or, for the sake of argument only, Chao, would not necessarily have the same phenotype as platelets activated by the specific list of

agents set forth in the claims. Therefore there is no basis for concluding that the microparticles produced according to Chao and according to the invention are the same.

Therefore, because Chao's composition incorporates the supernatant and the claimed invention does not, and because the microparticles of Chao and the microparticles of the invention are not inherently the same, Chao does not anticipate the claims, so that the rejection should be removed.

4. The Claims Are Not Obvious

Claims 17-23 are rejected under 35 U.S.C. §103(a) as obvious over Knighton taken with Chao, United States Patent No. 5,552,290 by Michelson et al. ("Michelson") and United States Patent No. 5,697,980 by Otani et al. ("Otani"). The Examiner states:

> It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to add various carriers, fillings, biodegradable materials and devices including titanium, apatite and organic polymers to modify the drug compositions taught by [Knighton] and/or [Chao] as suggested by [Knighton] with a reasonable expectation of success in wound healing because the claimed carriers and materials are known and used for making artificial filling, carriers and medical devices as adequately demonstrated by [Otani]. One of skill in the art would have been motivated to adjust carrier compositions of [Knighton] and of [Chao] with regard to a mode of administration for the expected benefits in wound healing and/or bleeding reduction as provided by microparticles derived from blood platelets. The knowledge about the use of various platelet activating agents for making and collecting the platelet derived microparticles is available in the prior art as adequately demonstrated by [Michelson].

Applicants assert that the claimed invention is not rendered obvious by the cited references, taken in any combination or individually. As set forth above, the difference between the claimed invention and the primary references cited, Knighton and Chao, is that the cited references utilize the supernatant, whereas the present invention separates the microparticles *from* the supernatant and does not use the supernatant. This is a relevant difference in that the

supernatant would be expected to contain factors that may be useful in wound healing. For example, Applicants invite the Examiner's attention to Exhibit C, Gemmell et al., 1993, J. Biol. Chem. 268:14586-14589, which in the background states:

> Platelet activation elicits a variety of physiologic cellular responses including shape change, intracellular ion fluxes. induction of coupling responses, biochemical membrane alterations, induction of membrane procoagulant activity, release of granule contents, and initiation of aggregation. The release from the cell surface of small membrane vesicles or microparticles should be added to the list.

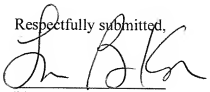
Thus, the supernatant utilized by Knighton would be expected to include, for example, platelet granule contents, and it would not be reasonably expected that the composition of the invention, which does not utilize the supernatant, would be effective. Applicants continue to dispute that Chao teaches activated platelets, for reasons set forth above, but even if, for the sake of argument, Chao teaches activation, the fact that Chao uses the supernatant does not render obvious the presently claimed invention, which does not use the supernatant. The disclosure of Otani as regards biomaterials and/or the disclosure of Michelson regarding microparticles does not remedy this defect.

Accordingly, the cited references do not render the claimed invention obvious, so that the rejection should be removed.

CONCLUSION

For all the foregoing reasons, the rejections should be removed and the claims should be allowed to issue.

Respectfully submitted,



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